

SHORT REPORT

Self-reported goiter is associated with a significantly increased risk of gastric noncardia adenocarcinoma in a large population-based Chinese cohort

Christian C. Abnet^{1*}, Jin-Hu Fan², Farin Kamangar¹, Xiu-Di Sun², Philip R. Taylor¹, Jian-Song Ren², Steven D. Mark¹, Ping Zhao², Joseph F. Fraumeni, Jr.¹, You-Lin Qiao^{2*} and Sanford M. Dawsey¹

¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD

²Cancer Institute, Chinese Academy of Medical Sciences, Beijing, People's Republic of China

Iodine is concentrated by the gastric mucosa, where it may act as an antioxidant. Therefore, iodine deficiency, and its sequelae goiter, may be associated with an increased risk of gastric cancer. We examined the association between self-reported goiter and upper gastrointestinal cancer in a Chinese cohort of 29,584 adults. Using multivariate adjusted Cox models, we found goiter associated with a significantly increased risk of gastric noncardia adenocarcinoma, HR (95% CI) 2.04 (1.01, 4.11) and nonsignificantly with gastric cardia adenocarcinoma, HR (95% CI) 1.45 (0.91, 2.30). We also found a borderline, insignificant increased risk of esophageal squamous cell carcinoma, HR (95% CI) 1.37 (0.97, 1.94). Our findings are consistent with the hypothesis that iodine deficiency is associated with an increased risk of gastric cancer.

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Iodine deficiency diseases and goiter remain prevalent in many parts of the world, while gastric cancer is the fourth most frequent cancer worldwide.¹ Venturi *et al.* have hypothesized that iodine deficiency is causally associated with gastric cancer.² Gastric tissue concentrates iodine, where it may act as an antioxidant. Increased iodine intake may explain the reported association between consumption of seafood and lower risk of gastric cancer.² A recent case-control study from an area of Turkey with endemic iodine deficiency disease reported that subjects with gastric cancer had a higher prevalence of goiter and autoimmune thyroid disease than healthy controls had.³ Other studies have also demonstrated that gastric cancer patients excrete more iodine than healthy controls,⁴ even when both are consuming iodized salt, and that gastric cancer tissue has a lower iodine concentration than surrounding normal tissue.⁵

Gastric cancer was the leading cause of cancer death in the US until the 1930s, but began to decline rapidly thereafter. This has generally been attributed to the advent of refrigeration, which increased the availability of fresh fruits and vegetables and reduced the need for cured, salted, and pickled foods,⁶ and the introduction of better sanitation practices, which was probably responsible for the reduced prevalence of *Helicobacter pylori* infection.⁷ Iodine-fortified salt was introduced in the US in 1924 to help prevent iodine deficiency diseases, and its use was widespread by 1950. Therefore, if the underlying hypothesis is correct, iodine fortification in the US may also have contributed to the decline in gastric cancer incidence.

Alternatively, some goitrogens might also cause gastric cancer. Examples include methylanthracene and other polycyclic aromatic hydrocarbons and bacterial contamination of water supplies, which can lead to high concentrations of *N*-nitroso compounds.⁸ Thus, any association between goiter and gastric cancer could result from goitrogens or other confounding exposures, rather than as a consequence of iodine deficiency.

Material and methods

We previously reported the methods for the Linxian General Population Nutrition Intervention Trial.^{9–11} The trial and subse-

quent follow-up were approved by the ethical committees of both the Cancer Institute, Chinese Academy of Medical Sciences and the National Cancer Institute and subjects provided informed consent. The underlying study was a fractional 2³ factorial randomized controlled trial of four different vitamin and mineral combinations in 29,584 adults from a Chinese population with very high rates of esophageal and gastric cancers. The intervention lasted 5.25 years (1986–1991) and none of the supplements contained iodine. The cohort has been followed continuously up to the present time. Follow-up time was calculated as the number of days from trial baseline in May 1986 through incidence of any cancer, death, or May 2001. Case ascertainment is essentially complete with <1% of subjects lost to follow-up, and at least 85% of cases were verified by a review panel of senior Chinese and American experts. Linxian has very high rates of esophageal squamous cell carcinoma and gastric cardia adenocarcinoma and only moderate rates of gastric noncardia adenocarcinoma. Because of this and the differences in the etiology of cancer at the two gastric cancer sites, we typically report associations with gastric cancer at the two sites separately. These three cancers account for 85% of all incident cancers in this cohort.

At study baseline, subjects completed a questionnaire regarding habits, personal characteristics, diet and medical history including the question “have you ever had a diagnosis of goiter?”.

We examined potential confounding variables selected because of their known association with stomach cancer or other upper GI cancers in this cohort and potential association with goiter (*e.g.*, egg consumption or water source). Data were tabulated by goiter status, and univariate associations were tested using Wilcoxon rank sum tests and Fisher's exact tests for continuous and categorical variables, respectively. Hazard ratios and 95% confidence intervals come from multivariate Cox proportional hazards models. We added variables one at a time and retained variables that changed the beta coefficient for goiter by $\geq 10\%$ or were independently associated with cancer. We tested for and found no evidence of nonproportionality in our Cox models. All *p* values come from 2-sided tests. We considered associations with *p* values < 0.05 or confidence intervals that exclude 1.0 as statistically significant.

Results

Table I presents selected baseline characteristics of the General Population Trial subjects, by self-reported history of goiter. Sub-

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*Correspondence to: Christian Abnet, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, Room 305, MSC 7232, Bethesda, MD 20892. Fax: 301-496-6829 E-mail: abnetc@mail.nih.gov or You-Lin Qiao, Department of Cancer Epidemiology, Cancer Institute, Chinese Academy of Medical Sciences, 17 S. Panjiayuan Lane, Beijing, 100021, People's Republic of China. E-mail: qiaoy@public.bta.net.cn

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TABLE 1 – NUTRITION INTERVENTION TRIAL (GENERAL POPULATION COHORT BASELINE SUBJECT CHARACTERISTICS AND CANCER INCIDENCE, 1986–2001) BY SELF-REPORTED HISTORY OF GOITER

Variable	Goiter = no	Goiter = yes	p-value ¹
Characteristic			
Number	29,027	425	–
Age at baseline, years	52 [44, 59] ²	49 [43, 56]	<0.0001
Sex: male, <i>N</i>	12,970 (44.7) ³	143 (33.7)	<0.0001
Ever regularly smoke tobacco: yes, <i>N</i>	8,777 (30.3)	100 (23.5)	0.0024
BMI, kg/m ²	21.7 [20.3, 23.3]	21.9 [20.4, 23.5]	0.085
Any alcohol in previous 12 months: yes, <i>N</i>	6,810 (23.5)	99 (23.3)	1.00
Family history of stomach cancer: yes, <i>N</i>	885 (3.1)	20 (4.7)	0.063
Family history of esophageal cancer: yes, <i>N</i>	7,941 (27.4)	132 (31.1)	0.10
Eggs consumed/year, <i>N</i>	10 [2, 36]	12 [2, 24]	0.31
Piped water: yes, <i>N</i>	7,171 (24.7)	96 (22.6)	0.34
Incident cancer cases			
Esophageal squamous cell carcinoma, <i>N</i>	1,916 (6.6)	33 (7.8)	0.33
Gastric cardia adenocarcinoma, <i>N</i>	1,059 (3.7)	18 (4.2)	0.51
Gastric noncardia adenocarcinoma, <i>N</i>	355 (1.2)	8 (1.9)	0.26

¹*p*-values come from Wilcoxon rank sum test (continuous variables) and Fisher's exact test (categorical variables). ²Values in square brackets indicate median, IQR. ³Values in parentheses indicate percentages.

TABLE 2 – MULTIVARIATE-ADJUSTED¹ HAZARD RATIOS AND 95% CONFIDENCE INTERVALS (CI) FOR THE ASSOCIATION BETWEEN SELF-REPORTED HISTORY OF GOITER AND INCIDENT UPPER GI CANCERS IN THE NUTRITION INTERVENTION TRIAL, GENERAL POPULATION COHORT

Cancer site	HR	95% CI	p-value
Esophageal squamous cell carcinoma	1.37	0.97, 1.94	0.073
Gastric cardia adenocarcinoma	1.45	0.91, 2.30	0.12
Gastric noncardia adenocarcinoma	2.04	1.01, 4.11	0.047

¹Cox models with adjustments for age, sex, ever regular tobacco smoking, BMI and family history of stomach cancer.

jects with goiter were significantly younger, more likely female and less likely to have smoked tobacco regularly. Subjects reporting goiter also had nonsignificantly higher BMI, and a higher proportion reported a family history of stomach cancer. We found no significant differences by baseline goiter status in the proportion of subjects who developed any of the three upper GI cancers at the end of follow-up.

After adjusting for age, sex, tobacco smoking, BMI and family history of stomach cancer, we found that a self-reported history of goiter was associated with a significant 2-fold increased risk of gastric noncardia adenocarcinoma (HR (95% CI) 2.04 (1.01, 4.11)). Although nonsignificant at *p* < 0.05, we found increased risk of and gastric cardia adenocarcinoma (1.45 (0.91, 2.30)) and esophageal squamous cell carcinoma (1.37 (0.97, 1.94)). We also examined the association between goiter and total gastric cancer and found a significant association, HR (95% CI) 1.59 (1.08, 2.34), *p* = 0.020.

Discussion

Our finding is consistent with the hypothesis that iodine deficiency, as reflected by goiter, is associated with an increased risk of gastric cancer. When tested without adjustment, the associations between goiter and cancer were nonsignificant, but the asso-

ciations became significant after adjusting for age and sex. Notably, subjects reporting goiter at baseline had a median age 3 years less than the cohort as a whole. The reason for this difference is unknown. The other factors included in the final model had little effect on the goiter hazard ratios. The narrow confidence interval for the association with esophageal squamous cell carcinoma barely includes 1.0 and the low *p*-value (0.073) provides some evidence that goiter is associated with increased risk of this cancer as well (Table 2).

Failure to adjust for confounders is a potential explanation of all observational epidemiologic findings. The most important potential unmeasured confounder for gastric cancer in this study was *Helicobacter pylori* infection, a major cause of gastric cancer. We previously reported that *H. pylori* is associated with significantly increased risk of both gastric cardia (OR = 1.87) and gastric noncardia adenocarcinoma (OR = 2.29) in this population.¹² We tested for and found no association between *H. pylori* seropositivity and goiter in a subset of our population that had information on *H. pylori* seropositivity (data not shown). Therefore, we believe that confounding by *H. pylori* is unlikely to explain the observed association between goiter and risk of gastric cancer. However, whether the associations are truly due to iodine deficiency, exposure to other goitrogens that also increase the risk of cancer, other unmeasured confounders, or chance cannot be assessed in this analysis.

Mild iodine deficiency is common in Linxian. About 2% of the study population self-reported a history of goiter at study baseline. Iodine fortification started in this population in the 1970s, but full coverage was not achieved until after 1994. Self-reported goiter as a marker of iodine deficiency is likely to have low sensitivity but high specificity. We cannot assess whether the degree of iodine deficiency necessary to induce a goiter is equivalent to that which may be associated with increased risk of upper GI cancer. Further work which examines the consistency of the association and which better defines the level of iodine deficiency associated with increased risk of upper GI cancer will be necessary before the fraction of gastric cancer associated with iodine deficiency can be estimated.

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